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Alveolar Macrophage Dysfunction and Chronic Alcohol Use

Time to Think about Zinc

As the resident professional phagocyte in the lungs, the alveolar macrophage plays a central role in the maintenance of alveolar homeostasis, lung host defense, and immune regulation. During health, the alveolar macrophage operates both as an antiinflammatory effector cell that silently removes particulate debris and microbial organisms from the air spaces, and as a sentinel that initiates inflammatory responses when host defense systems are overwhelmed. During inflammation the role of the alveolar macrophage further expands to include clearance of apoptotic cells from sites of injury and initiation of antiinflammatory and tissue repair programs. A growing body of evidence suggests that chronic ingestion of alcohol impairs many of these essential functions, including phagocytosis of bacteria and ingestion of apoptotic cells. It is therefore not surprising that chronic alcohol use places individuals at increased risk for pneumonia and development of acute respiratory distress syndrome (ARDS) (1, 2). In this issue of the *Journal*, Mehta and colleagues (pp. 716–723) add to their previous work on alcohol-related lung disease by systematically characterizing alveolar macrophages isolated from individuals with alcohol use disorder and carefully matched control subjects (3). In doing so, they highlight important mechanisms that underpin alveolar macrophage dysfunction in the alcoholic lung. These include intracellular zinc deficiency, altered redox state, and impaired signaling through the granulocyte–monocyte colony–stimulating factor (GM-CSF) receptor.

To understand how these factors affect macrophage function, it is important to recognize that macrophage programming is directly influenced by the environment in which the macrophage resides (4). In this regard, the alveolar environment is extraordinarily unique. As an extraepithelial compartment that communicates directly with the atmosphere, the alveolus contains high partial pressures of oxygen, large amounts of surfactant lipids and protein, and the highest concentrations of GM-CSF found anywhere in the body (5, 6). Intriguingly, chronic alcohol ingestion leads to marked alterations in the alveolar environment, including decreased surfactant production by alveolar type II cells, depletion of glutathione in the epithelial lining fluid (thereby promoting an oxidative environment), and enhanced expression and activation of transforming growth factor- β (7–9). Perhaps even more importantly, chronic alcohol ingestion leads to down-regulation of the GM-CSF receptor on alveolar macrophages, resulting in decreased expression and nuclear binding of the PU.1 master transcription factor (10, 11).

The importance of GM-CSF as a central regulator of macrophage function is demonstrated most conclusively in the context of pulmonary alveolar proteinosis. In the most common form of this disease, circulating autoantibodies to GM-CSF are present, resulting in impaired macrophage activation, reduced phagocytic capacity, and defective bacterial killing. Reduced expression of GM-CSF receptor subunits and impaired receptor signaling are well documented in rodent models of chronic alcohol ingestion;

it is therefore not surprising that similar defects in alveolar macrophage function (albeit less severe) are present. Accordingly, pharmacologic administration of recombinant GM-CSF to alcohol-fed rats appears to reverse many of these defects (11). In their current work, Mehta and colleagues demonstrate for the first time that chronic alcohol use down-regulates the GM-CSF receptor β -subunit in human alveolar macrophages (3). These findings add to an already substantial body of evidence that implicates impaired GM-CSF signaling as a central pathophysiologic abnormality in alcohol-related lung disease and points to recombinant GM-CSF as an attractive agent that could potentially prevent (or treat) pneumonia and ARDS in patients with alcohol use disorders.

A second potential therapy for patients with alcohol-related lung disease is zinc. Zinc is an essential cofactor for over 300 metallo-enzymes and is important for cellular homeostasis, proliferative responses, and redox balance. In their current work, Mehta and colleagues demonstrate that macrophages from subjects with alcohol use disorder have reduced intracellular levels of zinc (3). Curiously, serum zinc levels in these individuals were similar to those of healthy control subjects. As with other aforementioned abnormalities in macrophage function, this seeming discrepancy can be explained on the basis of alcohol-induced perturbations in the alveolar environment. Within the alveolar space, zinc is transported into alveolar epithelial cells and macrophages by the zinc transporter, ZIP₄ (12). Importantly, high levels of transforming growth factor- β in the alcoholic lung appear to inhibit expression of ZIP₄, through a mechanism that involves Krüppel-like factor 4 (KLF₄). Intriguingly, KLF₄ expression is induced by the PU.1 master transcription factor. Hence, zinc transport may be further reduced in the alcoholic lung as a result of impaired GM-CSF receptor signaling (13).

Previous work by Mehta and colleagues demonstrates that supplementation of zinc to alcohol-fed rats increases PU.1 expression in alveolar macrophages, reverses alveolar macrophage dysfunction, and enhances bacterial clearance (14). The authors' current work builds on these findings and demonstrates a similar effect in cultured alveolar macrophages isolated from chronic alcohol consumers. Taken as a whole, these observations suggest the exciting possibility that dietary zinc supplementation could be effective at preventing or ameliorating critical illness in patients with alcohol use disorder. Clearly additional clinical studies are needed to test this hypothesis. Given the high burden of alcohol use in society and the fact that alcohol abuse is responsible for up to 40% of intensive care unit admissions in the United States (1, 2), the current study should encourage us to think about zinc.

Author disclosures are available with the text of this article at www.atsjournals.org.

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Envisioning Sophisticated Electronic Health Records through the Lens of Health Care Reform

One of the least publicly discussed aims of recent health care reform legislation in the United States is to vastly improve the utility of electronic health records (EHRs) for clinical practice and research. If successfully implemented, EHRs will become platforms for the bidirectional flow of information from patients and providers to researchers and policy-makers, thus creating a nationwide learning health system (1). Significant steps toward improving EHRs so that greater value can be extracted from them were made with two pieces of legislation, the Health Information Technology for Economic and Clinical Health (HITECH) Act, passed as part of the broader American Recovery and Reinvestment Act of 2009, and the Patient Protection and Affordable Care Act (PPACA) of 2010 (2, 3). These laws, and setting up a learning health system, will have a profound impact on the clinical and research communities within pulmonary, critical care, and sleep medicine. In this editorial, we will review the benefits of using enhanced EHRs to create “smart” health systems, discuss the ways in which health reform supports the development of sophisticated EHRs, and outline how these changes will impact the practice of pulmonary, critical care, and sleep medicine.

The development of EHRs in the United States has been slow and piecemeal compared with other industrialized nations (4). As recently as 2008, less than one in five hospitals or physician practices had functional EHRs (5, 6). Barriers to EHR implementation included a lack of economic incentives, the technical complexity of EHRs, problems with interoperability between systems, and privacy concerns (4). It is no surprise, therefore, that the EHR implementation process adhered to the systemic vagaries of the American

health care marketplace, where competitive market forces led to a fragmented and patchwork health delivery system.

Indeed, implementation has moved at a pace far from desirable even though there is evidence for improved clinical and research capabilities at institutions where enhanced EHRs were implemented. The Department of Veterans Affairs (VA)’s Veterans Health Information Systems and Technology Architecture (VistA) system is one of the first enhanced EHR systems implemented in the United States. It contains integrated information exchange functionality (patient information can be accessed easily by any VA provider) as well as computerized physician order entry, quality data measurement, clinical decision support, and alerts and reminders. In addition, VistA incorporates a new point-of-care clinical trial design that streamlines the cumbersome clinical trial process and allows for easy transitions from research study to decision support. This functionality thus merges evidence discovery with clinical care, as is called for by a learning health system (7). By achieving near-universal EHR adoption, the VA significantly improved quality of care, resulting in a conservatively measured net value of more than \$3 billion as of 2007 (8).

Other EHRs have demonstrated additional advanced capabilities. As large data repositories, EHRs have been used to identify predictors of missed opportunities for the early diagnosis of lung cancer and to enable the early detection of the 2009 novel influenza A (H1N1) pandemic, including comorbidity identification and geographic tracking (9, 10). EHRs can provide clinical decision support to improve the timing of code status documentation in patients with advanced lung cancer and to issue guideline-based reminders to clinicians to test for α_1 -antitrypsin deficiency on the basis of automated recognition of airflow obstruction (11, 12). In addition, EHRs have been used for patient triage and resource